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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/820,320	03/28/2001	Henry E. Young	1304-1-019 CIP1	4118

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/820,320	YOUNG ET AL.	
	Examiner	Art Unit	
	Thai-An N Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-28 and 31-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-28 and 31-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7/3/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Amendment, filed 9/15/03, has been entered. Claims 1-23, 29 and 30 have been cancelled. Claims 24-28, 31 and 32 have been amended. Claims 33 and 34 have been added. Claims 24-28 and 31-34 are pending and under current examination.

Priority

The priority information has been updated.

Specification

The amendment to the specification has been entered.

Information Disclosure Statement

Applicants' Information Disclosure Statement, filed 7/3/2003 has been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-28 and 31-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of transplanting

allogeneic or autologous pluripotent embryonic-like stem cells in a knee comprising introducing into the knee pluripotent embryonic-like stem cells, which have been cultured on a matrix or substrate for at least 2 weeks *in vitro*, wherein the cells are derived from non-embryonic or postnatal animal cells or tissue, capable of self-renewal and capable of differentiation to cells of endodermal, ectodermal and mesodermal lineages *in vitro*, wherein the stem cells proliferate and differentiate into cartilage and bone in the knee. The specification does not reasonably provide enablement for methods of transplanting the pluripotent embryonic-like stem cells in a host, methods of *in vivo* administration of a protein or gene of interest into a mammal by administration of transfected pluripotent embryonic-like stem cells, methods of preventing or treating cellular debilitations, derangements, dysfunctions or other disease states in mammals by administration of the pluripotent embryonic-like stem cells, and pharmaceutical compositions comprising the pluripotent embryonic-like stem cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants argue that submit that the specification provides guidance and examples that, combined with the significant knowledge and skill of the skilled artisan, and importantly considering the novel and remarkable capabilities and characteristics of the pluripotent embryonic-like stem cells of the instant invention, enable the practice of the invention, and in particular enable the use of the stem

cells of the invention in methods of transplantation, treatment and gene therapy, without undue experimentation. See p. 8 of the Response.

Applicants' arguments have been considered, however, they are not found to be persuasive. Firstly, the embryonic-like stem cells of the instant invention are shown to differentiate into endodermal, ectodermal and mesodermal lineages *in vitro*, however, the specification fails to show the differentiation of these cells into the three lineages when introduced *in vivo*. For example, the multiple phenotypes described from the differentiation of 3T3 cells formed mesodermal phenotypes [see example 5]. Example 23 describes the *in vivo* assessment of neural phenotypes by the transplantation of the claimed cells into the striatum of adult rats and then the cells were merely tested for migration and expression of GFP. Example 26 provides evidence that the rabbit stem cells can produce cartilage and bone, which are cells of mesodermal origin. As such, the specification fails to show that the claimed pluripotent embryonic-like stem cells of the instant invention are capable of differentiating into endodermal, ectodermal and mesodermal lineages *in vivo*.

With regard to Applicants' argument that it is unnecessary to provide working examples of all cell and/or tissue types and all therapies or defects so long as there is a sufficient and enabling disclosure to guide the skilled artisan. Applicants argue that in addition to the teaching of the Specification and the significant knowledge of the skilled artisan, the prior art provides teaching and methods for the differentiation and characterization of cells and tissues from

ectodermal, endodermal and mesodermal stem cells, which teaching is clearly applicable to the embryonic-like stem cells as they are precursors of these more restricted and further differentiated stem cells. See p. 9 of the Response.

This argument is not found to be persuasive. The claims are directed to methods of transplanting pluripotent embryonic-like stem cells into a host, and methods of preventing or treating cellular debilitations, derangements, dysfunctions, or other disease states in mammals. Although working examples are not required for a disclosure to be enabling, the lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP §2164.02. The Examiner has clearly set forth the unpredictable and undeveloped state of art of cellular transplantation of stem cells and gene therapy. See pp. 9-17 of the prior Office action. Applicants address such arguments as follows: Applicants argue that the pluripotent embryonic-like stem cells of the instant invention are isolated from non-embryonic or postnatal (or even adult sources), therefore the need for stem cells to be derived from allogeneic sources [see Strom, cited previously] or screening donor cells [see Henningson and Prelle, cited previously], may be avoided because the instant stem cells may be obtained as an autologous source. See p. 10, 1st ¶ of the Response. In response, it is noted that the claims do not limit the embryonic-like stem cells of the instant invention to any particular source, and certainly not to autologous sources. The specification fails to provide teachings to overcome the art-recognized

unpredictabilities with regard to transplantation of stem cells, such as the directed differentiation of stem cells [see Zandstra, cited previously], and the requirement for the cells to be immune tolerant [see Strom]. Applicants point to Example 12, wherein rat pluripotent embryonic-like stem cells when implanted in outbred rats do not induce graft versus host disease, Example 15 that demonstrates that human pluripotent embryonic-like stem cells can be co-transplanted into mice and shown to populate the bone marrow, and Example 18, which shows that genomically labeled beta-gal rat pluripotent embryonic-like stem cells were administered and tested *in vivo* in a hindlimb ischemic model rat, wherein it was found that labeled rat cells were incorporated in the hindlimb at the ischemic site. Applicants argue that this demonstrates that immunological rejection was not observed in these *in vivo* studies, thus, the specification demonstrates that the pluripotent stem cells of the present invention can be transplanted to obtain appropriate integration in a desired site and can successfully avoid the host's immune response.

Applicants' arguments have been considered, but are not found to be persuasive. The rats described in Example 12 are allogeneic. Kuby [*Immunology*, 1992, p. 533] defines allogeneic as, "genetic variation between members of the same species." Although the rats are not inbred [*i.e.*, syngeneic], they are members of the same species. The art cited previously by the Examiner clearly teaches that one of the requirements for successful cellular transplantation therapy utilizing stem cells is using cells from an allogeneic source. The claims, as broadly written, encompass

the transplantation of stem cells from one species to another, xenotransplantation. The state of the art of cellular transplantation is such that transplantation of cells from different species is not predictable [see Strom, cited previously]. With regard to Example 15, the animals used were immune-deficient NOD/SCID mice [see p. 254, lines 1-5] and in Example 18, the animals used were rat SCID animals [see p. 264, lines 12-13]. Accordingly, there would be no expectation of an immune response or rejection in these animals. Thus, the specification fails to provide teachings or guidance with particularity to show that the pluripotent stem cells of the instant invention would not be rejected in methods of xenogeneic cellular transplantation, which are broadly encompassed by the claims and which the state of the art clearly teaches as unpredictable.

Applicants argue that while some experimentation to use the embryonic-like stem cells in the claimed methods would be necessary, such experimentation would utilize well-known and standard skill and would not constitute undue experimentation. Applicants argue that the specification provides sufficient teachings and guidance for the skilled artisan, that a number of working examples are provided, that the extent of the prior art available to those skilled in the art with regard to the use of stem cells and practice of the claimed methods was significant at the time of filing, and that the breadth of the claims is commensurate with the significant skill of those in the art and the significant applicability of the

stem cells of the invention to use in various methods. See pp. 11-12 of the Response.

Applicants' arguments have been considered, but are not found persuasive. It is reiterated that the claims as broadly written are drawn to treatment of any disease utilizing pluripotent embryonic-like stem cells, by any mode of administration. However, the specification fails to provide teachings or guidance as to what levels or amounts of pluripotent embryonic-like stem cells would correspond to a therapeutic effect. The specification broadly teaches uses for the claimed stem cells, however, does not provide teachings or guidance to show that the stem cells would be capable of functioning in an appropriate manner in an appropriate physiological setting.

The working examples provided by the specification teach the implantation of felt which had been seeded with pluripotent embryonic-like stem cells into an osteochondral defect in the knee of rabbits. Analysis of the control versus the animals receiving the stem cells that had been seeded on felt for 2 weeks prior to transplantation showed consistent regeneration with integration of the tissue in the defect to the host cartilage, whereas the animals receiving stem cells that had been cultured for 24 hours on felt had highly variable histology, and that some defects contained connective tissue or fat, where others had fibrocartilage and bone formation. See p. 296, lines 11-30. The specification teaches that there were significant differences in the improvement of mechanical strength between the

control animals and the animals received the stem cells, and a significant difference between the mechanical strength of the defects treated with stem cells cultured for 24 hours versus defects treated with stem cells for 2 weeks. See p. 298, Table 22 and lines 22-28. Accordingly, the specification provides specific *in vivo* teachings with regard to the generation of cartilage and bone in a knee defect and improvement of mechanical strength of the knee, when stem cells that had been cultured for 2 weeks on felt are introduced into the defect. However, the specification fails to provide teachings to enable the breadth of the claims, which are directed to methods of repair of any type of tissue by introduction of pluripotent embryonic-like stem cells, and methods of treatment or preventing any disease in any mammal by administering pluripotent embryonic-like stem cells. Furthermore, the specification fails to provide teachings or evidence with regard to the prevention of any disease, as required by the claims. The specification fails to show that the pluripotent embryonic-like stem cells are capable of differentiation into cells of endodermal, ectodermal and mesodermal lineages *in vivo*, as the working examples only provide evidence of differentiation of the stem cells into mesodermal lineage cells.

With regard to the embodiments of the claimed invention directed to gene therapy [*e.g.*, claim 26], Applicants have failed to provide teachings, guidance or arguments to overcome the previously stated unpredictabilities associated with the gene therapy art. In the prior Office action, the Examiner has provided teachings to

show that the state of the art of gene therapy is both undeveloped and unpredictable [see pp. 13-17 of the prior Office action, particularly Palù and Romano]. Unpredictable factors such as predictably achieving levels and duration of gene expression have not been overcome by routine experimentation. For example, Palù teaches that better delivery systems, sustained expression of a therapeutic gene in the appropriate cells are imperative to achieving predictable therapeutic results. The specification fails to provide teachings or guidance to show that a transfected embryonic-like stem cell of the instant invention, when used in methods of *in vivo* administration, would provide therapy in a subject. The specification's teachings are directed to marker genes, particularly βgal expression, but the specification fails to provide teachings or guidance to overcome the unpredictabilities associated with the gene therapy art. For example, a therapeutic gene must be expressed in sufficient amounts to be therapeutic. The mere expression of a marker gene fails to provide any prediction of the expression of a therapeutic gene in an *in vivo*, as mere expression may not be sufficient to produce a therapeutic result.

The claims as broadly written, read on both *ex vivo* gene therapy and transfection of pluripotent embryonic-like stem cells *in vivo*, post transplantation. However, the state of the art of gene therapy is such that it would not be predictable with regard to transduction efficiency, delivery and maintenance of gene expression, which would be required for therapy. The specification fails to teach levels of

expression of any gene of interest necessary to show treatment of a disease. As such, with respect to the unpredictable nature of the gene therapy art, it would not be predictable if the transplantation of the claimed transfected stem cells would express and maintain expression for duration sufficient to be considered therapeutic in a subject. Note that the above-cited post-filing art clearly indicated an unpredictable status of gene therapy. Although specific vectors, promoters, genes and routes of administration may be, or might have been, effective for a specific disease which provides a specific therapeutic effect, gene therapy, as broad-based art, is clearly unpredictable in terms of achieving levels and durations of expression which would result in a therapeutic effect. As such, evidence pertaining to a specific vector, gene, promoter, route of administration, and therapeutic effect must be correlative to what is claimed, and in the instant application, a correlation and/or nexus cannot be drawn.

Accordingly, in view of the quantity of experimentation necessary to overcome the unpredictabilities associated with stem cell transplantation and gene therapy, the lack of direction or guidance provided by the specification to carry out stem cell therapy, as broadly claimed, for the treatment of any disease, the lack of direction or guidance provided by the specification to carry out gene therapy utilizing transfected stem cells, for the treatment of any disease, involving any particular vector, promoter, route of administration and subject, the breadth of the claims directed to any particular vector, promoter, route of administration or

subject, as well as the unpredictable and undeveloped state of the art of stem cell transplantation and gene therapy it would have required undue experimentation for one of skill in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The prior rejection of claims 24-32 as unclear is *withdrawn*. Applicants submit that the term "embryonic-like" stem cells is clear and provide the definition according to the specification and that the cells are embryonic-like because they have the capacity to differentiate into cells of any lineage, and that it is well-recognized that the embryo and its initial cells differentiate into all cells of the body (all lineages). See pp. 12-13, bridging ¶ of the Response. Applicants' argument is found persuasive by the Examiner.

The prior rejections of claim 26-31 are *withdrawn* in light of Applicants' amendments to the claims.

Claim Rejections - 35 USC § 102

The prior rejection of claims 24-32 under 35 U.S.C. 102(b) as being anticipated by Kiem *et al.* [**Blood**, 92(6):1878-1886, September 15, 1998] is *withdrawn* in view of Applicants' arguments and/or amendments to the claims.

The prior rejection of claims 27-31 under 35 U.S.C. 102(b) as being anticipated by Wang *et al.* [**Transplantation**, 65(2):188-192, January 1998] is *withdrawn* in view of Applicants' arguments and/or amendments to the claims.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Note: After January 13, 2004, the Examiner may be reached at (571) 272-0736. If the Examiner is unavailable, inquiries may be directed to Deborah Reynolds, SPE of Art Unit 1632, at (571) 272-0734.

TNT

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